# Behavior and Approximate Entropy of Right-eye Lateralization During Predation in the Music Frog

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**Abstract** Brain asymmetry for processing visual information is widespread in animals. However, it is still unknown how the complexity of the underlying neural network activities represents this asymmetrical pattern in the brain. In the present study, we investigated this complexity using the approximate entropy (ApEn) protocol for electroencephalogram (EEG) recordings from the forebrain and midbrain while the music frogs (*Nidirana daunchina*) attacked prey stimulus. The results showed that (1) more significant prey responses were evoked by the prey stimulus presented in the right visual field than that in the left visual field, consistent with the idea that right-eye preferences for predatory behaviors exist in animals including anurans; (2) in general, the ApEn value of the left hemisphere (especially the left mesencephalon) was greatest under various stimulus conditions, suggesting that visual lateralization could be reflected by the dynamics of underlying neural network activities and that the stable left-hemisphere dominance of EEG ApEn may play an important role in maintaining this brain asymmetry.

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## 1. Introduction

Lateralization in brain and/or behavior, i.e. brain asymmetry and/or preferential use of one side of the body, is a common trait among vertebrates and invertebrates, suggesting an evolutionarily ancient trait that may convey fitness benefits at both motor and cognitive levels (Bibost *et al.*, 2013). For example, strongly lateralized chimpanzees (*Pan troglodytes*) with left- or right- handedness for fishing termites with a stick are more efficient at extracting prey than those that repeatedly swap hands (McGrew and Marchant, 1999). It is likely that repeatedly using the same hand in the same task can entrain the animal to enhance motor performance because of enhanced dexterity through finer motor control and the recruitment of new neurons devoted to the task (Bibost *et al.*, 2013). Alternatively, laterality is also hypothesized to convey a cognitive advantage independently from motor entrainment. In animals, strongly lateralized individuals always exhibit better performance in cognitive tasks, such as problem solving in foraging contexts in different species of Australian parrots (Magat and Brown, 2009), schooling behavior in fish (*Girardinus falcatus*) (Bisazza and Dadda, 2005) and spatial memories in fruit flies (*Drosophila melanogaster*) (Pascual *et al.*, 2004). Since animals can process different information in different brain hemispheres, the dual processing hypothesis has been proposed that lateralized individuals may be capable of processing different sources of information simultaneously in each hemisphere of the brain (Rogers *et al.*, 2004). Accordingly, lateralization could potentially keep investment in brain tissue to a minimum, enhance cognitive efficiency, and increase fitness of individuals (Vallortigara, 2006; Vallortigara and Versace, 2017).

In animals, the preferential eye use for ecological activities,

one of the brain specialization phenomena during processing visual information, includes scanning for potential predators (Koboroff *et al.*, 2008; Martín *et al.*, 2010) and searching for prey (Bonati *et al.*, 2008; Robins and Rogers, 2004). Previous studies have shown that visual lateralization exists in some invertebrate species (Letzkus *et al.*, 2008; Schnell *et al.*, 2016) and numerous vertebrates including fish (Bisazza *et al.*, 2000), amphibians (Shen *et al.*, 2019), reptiles (Bonati *et al.*, 2013), birds (Vallortigara *et al.*, 2001), mammals (Thieltges *et al.*, 2011), non-human primates (Quaresmini *et al.*, 2014) and humans (Dimond *et al.*, 1976). In general, right-eye/left-hemisphere and left-eye/right-hemisphere advantages exist for identifying prey or food from other no-food items and identifying the predator, some conspecific fight or different emotional responses, respectively. Interestingly, an increase in visual asymmetry enhances success in visually guided foraging, i.e. the strength of lateralization correlates positively with efficiency in finding food (Güntürkün *et al.*, 2000). Moreover, visual lateralization may be associated with the individual's characteristics including vigilance and stress levels (Hook-Costigan and Rogers, 1998), their genders (Ariyomo and Watt, 2013), age and/or social environment (Besson *et al.*, 2017; Jozet-Alves *et al.*, 2012) as well as stimulus characteristics such as complexity or novelty (Robins and Rogers, 2006a; 2004).

The vertebrate brain is one of the most complex systems or network assemblies in the natural world, within which temporally and spatially multiscale structures provide the biophysical basis of brain functions (Bassett and Gazzaniga, 2011; Sporns, 2002). It seems logical to propose therefore that the complexity of the underlying neural network activities will be dynamic and can reflect the demands of information processing. Although processing visual information predominately through the left or right visual field is associated with a specialized function of the left and right brain (Rogers *et al.*, 2013), the complexity of the underlying neural network activity for visual lateralization is unclear. Since the optic nerve fibers in the anuran visual system decussate almost completely, visual information input received by either eye is processed primarily by contralateral neural circuits of the brain (Rogers, 2002). Moreover, prey attacks in anurans are typically primitive and stereotyped mechanical, thus, the anurans provide an excellent model to test the hypothesis that the complexity of the underlying neural network activity in the brain underlies right-eye advantage in predatory behaviors.

One way to monitor dynamic changes in the complexity in neural network activities for processing information is to analyze the electroencephalogram (EEG). Since all neural processes which occur in single neurons, neural circuits or brain areas are nonlinear (Babloyantz *et al.*, 1985; Jeong, 2004; Stam, 2005), many non-linear dynamics protocols have been successfully employed for EEG time-series analyses. Non-linear analysis can identify subtle changes in neural dynamics and providing novel interpretations of complex neural functions that could not otherwise be obtained using linear analysis (Babloyantz *et al.*, 1985; Stam, 2005). Among them, approximate entropy (ApEn) is a measure of irregularity or complexity of a dynamical system proposed by Pincus (Pincus, 1991), which is particularly effective for analyzing short and noisy time-series data and which can categorize a wide variety of systems ranging from multi periodic, stochastic to mixed systems (Pincus, 1995a; Pincus, 1995b). In short, ApEn is an indicator of randomness of time series, where its smaller value stands for less randomness/complexity. EEG entropy increases with experimental difficulty (Li *et al.*, 2016) and information processing demands (Hogan *et al.*, 2012; Sohn *et al.*, 2007; Zarjam *et al.*, 2013) as well as memory content (Namazi *et al.*, 2016). Thus, EEG ApEn is a sensitive discriminator of various cognitive conditions and/or different neurophysiological states (Fathillah *et al.*, 2017; Lippé *et al.*, 2009; Liu *et al.*, 2016; Talebi *et al.*, 2012; Zarjam *et al.*, 2013).

The present study measured the number of prey attacks and EEG ApEn during predatory behaviors in the music frog (*Nidirana daunchina*) in order to investigate whether eye preference exists in this species and how the complexity of the underlying neural network activities in the brain reflect this bias. We predicted that (1) presentations of prey-stimulus in the right visual field (RVF) would induce more predatory responses compared with presentations in the left visual field (LVF); and (2) the EEG ApEn of the left hemisphere would be significant greater than that of the right counterpart during predatory responses.

## 2. Materials and Methods

**2.1. Animals and surgery** In the present study, fourteen adult frogs (7 males and 7 females) captured from the Emei mountain area (29.60° N, 103.36° E, elevation of 1315 m above sea level) of Sichuan, China were used. The subjects were separated by sex and housed in two opaque plastic tanks (45 cm × 35 cm and 30 cm deep) containing mud and water. The tanks were placed in a room under controlled temperature (23℃ ± 1℃) and relative humidity (70%–80%) with a 12:12 light-dark cycle (lights on at 08:00). The animals were fed fresh live crickets every three days. At the time of surgery, the mean mass of them was 8.8 g ± 1.5 g (mean ± SD) and the length was 4.7 cm ± 0.3 cm.

The frog was deeply anesthetized via water bath in a 0.15% solution of tricaine methanesulfonate (MS-222) (Yue *et al.*, 2017) and the optimum depth of anesthesia was determined by loss of toe pinch response. Then, seven EEG electrodes (miniature stainless steel screws with 0.8 mm in diameter) were implanted

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inside the frog's skull and fixed with dental acrylic. Six of them were above the left and right sides of telencephalon (LT, RT), diencephalon (LD, RD) and mesencephalon (LM, RM) respectively, while the last one as the reference electrode (C) was implanted above the cerebellum (Figure 1). Before performing further experiments, each frog was housed individually for six days for recovery. After all experiments were finished, the frog was euthanized by immersion in MS-222 solution for a long time and the electrode locations were confirmed by injecting hematoxylin dye through the holes in the skull in which the recording electrodes had been implanted previously (see the electronic supplementary material, Figure S1). All efforts were made to minimize suffering.

**2.2. Test apparatus**  The design of the test apparatus was inspired by the previous studies in toads (Burghagen and Ewert, 1983; Robins and Rogers, 2004; Wachowitz and Ewert, 1996). Briefly, a cylindrical cup made of transparent polymethyl methacrylate (PMMA, 7 cm in diameter and 13 cm in high) was connected in the middle of a U-shaped frame (Figure 2). Under the cup, an electric turntable (20 cm in diameter and 5 cm in high) was placed and its velocity and rotation direction could be controlled by PC via WiFi. In addition, a white plastic wafer (22 cm in diameter) was adhered to the bottom of the cup for minimizing visual interference. A rod made of transparent PMMA was bent to form a right-angle and fixed on a board that was placed on the electric turntable. Furthermore, all above components were surrounded by a white opaque plastic cylinder (40 cm in diameter and 30 cm in high). A video camera with an infrared light source and motion detector (VSD-611H, Viesida Ltd, Shenzhen, China) was positioned centrally about 1 m above the test apparatus for recording behaviors of the animals.

**2.3. Visual stimulus and data acquisition**  Live crickets (about 1.5 cm in length) were used as prey stimuli (every live cricket for each frog) while fresh leaves with similar size of the crickets were used as control. The stimulus was hanged from the end of the rod using a white cotton thread (Figure 2). The distance between the stimulus and the cup was kept as about 3 cm.

The experiments were conducted in a sound proof and electromagnetically shielded chamber in which the light intensity was maintained at 0.07 lux. Before EEG signal recordings, the animal had to fast for at least five days. Then, it was placed in the cup containing water with a depth of about 1 cm and connected to the signal acquisition system (OmniPlex 64-D, Plexon, USA) for 10 min habituation. The stimulus was moved behind the subject via the rotating electric turntable. After the subject remained motionless for about one minute, the stimulus encircled the subject for five circles in either clockwise or anticlockwise direction at a constant velocity of

6.5°/sec. After a 2-min break, the same procedure was conducted again with the other direction. A 100 Hz low-pass filter was used for EEG signals with the notch filter of the amplifiers set to eliminate possible interference at 50 Hz. The sampling frequency was set to 1000 Hz. The experimenter should press a button as soon as the prey-catching response of the subject was evoked so that a red light emitting diode outside of the white opaque plastic cylinder lighted and a trigger would be sent to the signal acquisition system for synchronizing behavioral and EEG data. After the experiment was finished for each individual, the cup was washed and contained water again for the next subject. The animal was fed live crickets and returned to its home tank.

**2.4. Data processing**  In the present study, the predatory behaviors including turning of the body towards the visual stimulus and tongue-striking at it (hereafter referred to as 'turns' and 'strikes') were analyzed using frame-by-frame playback, similar to a previous study (Robins and Rogers, 2004). The numbers of 'strikes', 'turns' and 'strikes + turns' for LVF and RVF for each frog and each rotation direction were counted, respectively.

The protocols for calculating ApEn were described in the electronic supplementary material of the present study. Larger values of ApEn indicate greater fluctuation or irregularity in the time series while smaller values imply a stronger regularity or persistence (Pincus, 1991). The parameter $m$ (the embedding dimension of phase space) should be set to 1 or 2 ($m$ = 2 recommended) while $r$ (the tolerance, i.e. minimal distance between vectors) can range from 0.1 to 0.25 times the SD of the original data sequence (Pincus, 1991).

For EEG raw data, after band-pass filtering (0.5–45 Hz) and downsampling at 256 Hz, $r$ and $N$ were determined by calculating ApEn ($m$, $r$, $N$) with increasing $r$ from 0.1 to 0.4 SD in 0.05 steps and $N$ from 100 to 2000 in steps of 100 for randomly selected EEG segments while $m$ = 2. ApEn reached its maximum on a plateau when $N$ = 256 and this plateau was stable only when $r$ = 0.15 SD. Therefore, in the present study, ApEn for 3 s EEG data before predatory behaviors was computed using a slide window of $N$ = 256 (1 s EEG signal) with $r$ = 0.15 SD. Any epoch with an amplitude extremum beyond ±100 $\mu$V was discarded as artifact. Then, ApEn was averaged over 3 s for each stimulus, each visual field, each brain area and each subject. Since no predatory response was evoked by the control stimulus (leaf), both behavioral and EEG data for control were not analyzed.

**2.5. Statistical analyses**  The normality of distribution and homogeneity of variance for ApEn were estimated with the Shapiro-Wilk $W$ test and Levene's test, respectively. Since the behavioral data and ApEn values failed to meet the statistical
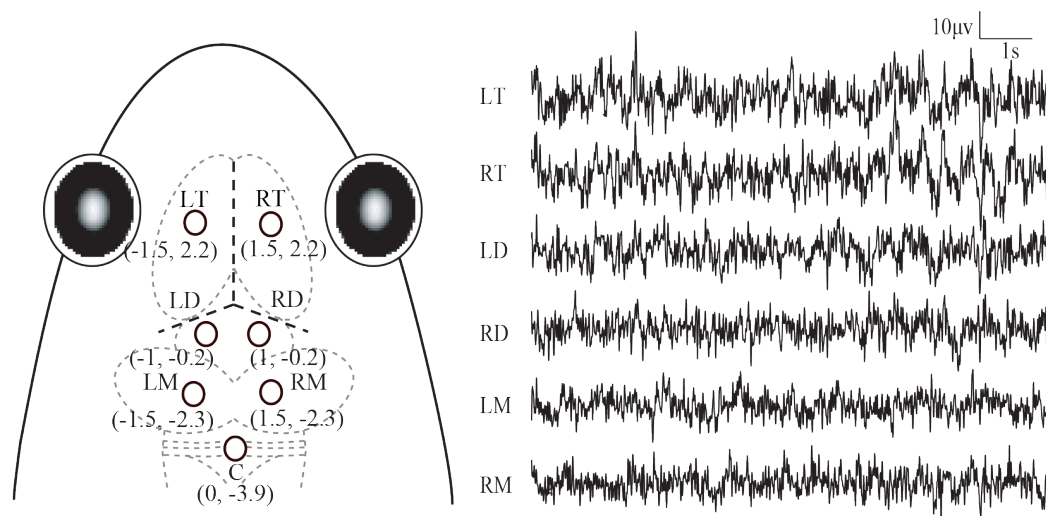
**Figure 1** Electrode placements and 10 s of typical EEG tracings for each brain area. The intersection of the three dashed lines in bold in the frog head denotes the intersection of suture lines corresponding to lambda. LT, RT, LD, RD, LM, RM denote the left and right sides of telencephalon, diencephalon and mesencephalon respectively; while C denotes the reference electrode implanted above the cerebellum.



**Figure 2** Schematic representation of the testing apparatus. Adapted from Shen *et al.*, 2019 with permission.

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assumptions, nonparametric tests were conducted. The Chi-square test was used to test the differences of numbers of predatory responses between left and right visual fields. ApEn values were statistically analyzed main effects using Friedman test with the factor of "brain area" (LT, RT, LD, RD, LM and RM) for each rotation direction and each visual field. While Wilcoxon Signed Ranks test was used for exploring differences between "brain area" when the main effects were significant. The same statistical method was adopted for comparing the differences between different visual fields and between different rotation directions. The Mann-whitney U test was used to test the differences of ApEn values between the sexes (males and females). SPSS software (release 21.0) was utilized for statistical analysis. A significance level of $P < 0.05$ was used for all comparisons.

## 3. Results

**3.1. Predatory behavior** When the data was pooled regardless of the rotation direction of the stimulus, more significant predatory responses were found in RVF compared with LVF for all subjects ($\chi^2 = 5.568$, $P = 0.018$; Figure 3A) and for males ($\chi^2 = 5.818$, $P = 0.016$; Figure 3A), but not for females. When the rotation direction was considered, more significant predatory responses presented in RVF compared with LVF for clockwise direction ($\chi^2 = 6.422$, $P = 0.011$; Figure 3A) but not anticlockwise direction.

**3.2. ApEn changes during predatory behaviors** For pooled data regardless of rotation direction of the stimulus and gender of the subjects, there were significant differences of ApEn values among different brain area for RVF ($\chi^2 = 13.224$; $P = 0.021$) and LVF ($\chi^2 = 13.044$; $P = 0.023$). For RVF, the ApEn value in the left mesencephalon was significantly higher than those in the telencephalon ($Z = -2.229$, $P = 0.026$ for the left telencephalon; $Z = -2.040$, $P = 0.041$ for the right telencephalon), the right diencephalon ($Z = -2.794$, $P = 0.005$) and the right mesencephalon ($Z = -2.229$, $P = 0.026$; Figure 3B). For LVF, the ApEn value in the left mesencephalon was significantly higher than those in the telencephalon ($Z = -2.481$, $P = 0.013$ for the left telencephalon; $Z = -2.341$, $P = 0.019$ for the right telencephalon) and the left diencephalon ($Z = -2.411$, $P = 0.016$); while the ApEn value in the left telencephalon was significantly lower than those in the right diencephalon ($Z = -2.621$, $P = 0.009$) and right mesencephalon ($Z = -2.132$, $P = 0.033$; Figure 3B). In addition, there was no significant difference of ApEn value between LVF and RVF.

For pooled data regardless of rotation direction, the results of Friedman test revealed that there were significant differences of ApEn values among different brain areas in LVF ($\chi^2 = 19.714$; $P = 0.001$) and RVF ($\chi^2 = 18.102$; $P = 0.003$) for males. For RVF,

the ApEn values in both sides of the mesencephalon and the left diencephalon were significantly higher than those in the telencephalon while the ApEn values in the right diencephalon was significantly higher than that in the left telencephalon ($P < 0.05$ Figure 3C). For LVF, the ApEn values in both sides of the mesencephalon and the right diencephalon were significantly higher than those in both sides of the telencephalon, while the ApEn value of the left mesencephalon was significantly higher than that in the left diencephalon, and that the value in the left diencephalon was significantly greater than that in the left telencephalon ($P < 0.05$; Figure 3C). However, the difference of ApEn values in each brain area was not significant between LVF and RVF. In addition, there was no significant difference in females.

With consideration of rotation direction, the results of Friedman test showed that significant differences of ApEn values presented among different brain areas in LVF ($\chi^2 = 12.111$; $P = 0.033$) and RVF ($\chi^2 = 15.224$; $P = 0.009$) when the prey stimulus was moved around the frogs in clockwise directions at constant velocity. For RVF, the ApEn values in the left mesencephalon was significantly higher than those in both sides of the telencephalon ($Z = -2.166$, $P = 0.030$ for the left telencephalon; $Z = -2.605$, $P = 0.009$ for the right counterpart) and the right diencephalon ($Z = -3.107$, $P = 0.002$; Figure 3D). For LVF, the ApEn values in the left mesencephalon was prominently greater than those in both sides of the telencephalon ($Z = -2.666$, $P = 0.008$ for the left telencephalon; $Z = -2.429$, $P = 0.015$ for the right counterpart) and the left diencephalon ($Z = -2.073$, $P = 0.038$; Figure 3D). However, when the prey stimulus was moved around the frogs in anticlockwise directions, there was no significant difference in LVF ($\chi^2 = 5.048$; $P = 0.410$) and RVF ($\chi^2 = 4.514$; $P = 0.478$; Figure 3D). There was no significant difference between LVF and RVF for a given rotation direction and brain area.

## 4. Discussion

**4.1. Right-eye preference for predatory behavior** The present results showed that the music frogs exhibited significant right-eye advantage for predatory responses when the prey-stimuli were moved into RVF, especially in a clockwise direction. These results were consistent with our recent study (Shen *et al.*, 2019) and were in accord with the idea that the right-hemifield of vision guides predatory responses in toads, such as *Bufo marinus*, *B. viridis* and *B. bufo Valsanzibio*, when the subjects were tested individually with automated moving prey-stimuli (Robins and Rogers, 2004; Vallortigara *et al.*, 1998). Predatory responses are more frequent when the prey stimuli is moved into RVF of toads (Robins and Rogers, 2004). In contrast, the toads tend to ignore such stimuli when they moved
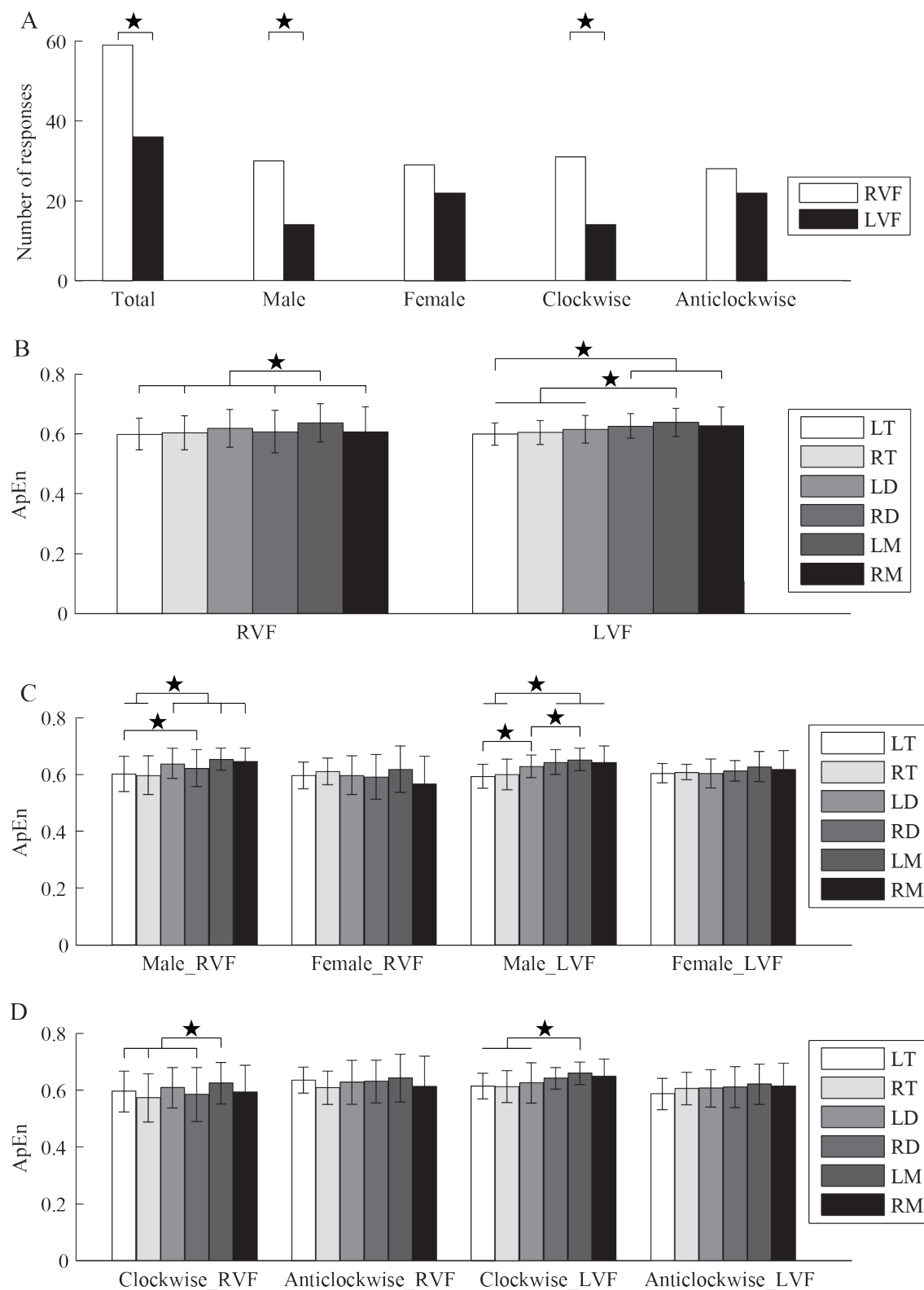
**Figure 3** The number of predatory responses for different conditions (A), means and standard deviations of EEG ApEn for the left and right visual fields (B), for males and females (C), and for different rotation directions (clockwise and anticlockwise; D). Filled stars denote that there were significant differences between the corresponding conditions ($P < 0.05$). 'RVF' and 'LVF' represent left and right visual fields. LT, RT, LD, RD, LM, RM denote the left and right sides of telencephalon, diencephalon and mesencephalon respectively.

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anticlockwise into LVF, and in this case, there is no significant bias between the left and right hemifields (Vallortigara *et al.*, 1998). Although only trend towards right-eye preferences for predatory responses but no statistical significance is achieved for South Australia green tree frog, *Litoria caerulea* (Robins and Rogers, 2006b), the findings including the present results suggest that right-eye advantage may be widespread in anurans, i.e. the left hemisphere devotes more resources to hunting when the prey moves clockwise.

The functional significance of visual lateralization may be to prevent conflict of response emission arising from visual inputs of two laterally placed (largely monocular) eyes (Andrew, 1983; Andrew *et al.*, 1982; Bradshaw and Rogers, 1992). Thus, an increase in visual asymmetry may enhance survival (Rogers *et al.*, 2004) and success in visually guided foraging (Güntürkün *et al.*, 2000). The left hemisphere, which primarily processes visual information from the right eye, controls responses that require considered manipulation of objects and discrimination between stimuli such as prey catching, foraging responses and visuo-spatial analysis centered on local features (Andrew and Rogers, 2002; Robins and Rogers, 2004; Vallortigara and Rogers, 2005; Vallortigara *et al.*, 1998). While the right hemisphere, which primarily processes visual information from the left eye, controls responses that are related to rapid reactions to changed visual surrounds and high levels of physiological arousal. These physiological conditions include aggressive responses to conspecifics, detection and avoidance of predators, and heightened sensitivity to novel stimuli. Accordingly, the asymmetry for predatory responses mediated by the right eye (the left side of brain) in anurans indicates that the anuran visual system can respond to certain basic or 'key' aspects of prey stimuli that require the subjects to make considered decisions based on complex visual cues (Robins and Rogers, 2004).

The right-eye lateralization for feeding responses has been identified widespread in vertebrates (Rogers *et al.*, 2013). Interestingly, similar visual lateralization exists in certain invertebrates such as cuttlefish (*Sepia officinalis*) (Jozet-Alves *et al.*, 2012; Schnell *et al.*, 2016) and honeybees (*Apis mellifera*) (Letzkus *et al.*, 2008). Moreover, there is even some suggestion of its existence as far back as the Cambrian period (Babcock, 1993). Thus, this brain asymmetry for predatory responses may be a common and relatively conservative brain specialization in animals. Preferential eye use reveals perceptual laterality which is likely to reflect the most basic and initial demands from which brain lateralization might have originally arisen (Bisazza *et al.*, 1997). In other words, specialization of the left hemisphere to control predatory responses has been evolved in the earliest vertebrates that use visual detection for prey (Andrew, 2002). In addition, since lateralization of swimming turns of responding

to external stimuli is related to lateralization of trunk muscle volume in fish (Heuts, 1999), similar relationship between right-eye preferences in predatory behavior and lateralization of the other part of the body in animals still need to be clarified.

## 4.2. Left-brain dominance of ApEn in predatory responses

The brain can be conceived as a complex network of coupling and interacting subsystems, and that higher brain functions depend upon effective processing and integration of information in this network (Stam, 2005). EEG complexity might reflect the interaction states of the brain, in which higher complexity is related to a larger number of separable oscillatory networks (Tononi and Edelman, 1998). The present results show that ApEn evoked by the prey-stimulus in the left hemisphere (especially the left mesencephalon) is greater than those in other brain areas, although some of the differences did not reach statistical significance. Brain complexity reflects the capacity of neural circuitry to support functional dynamics integrating specialized elements allowing perceptual, cognitive and behavioral states to simultaneously utilize multiple sensory modalities and submodalities (Sporns *et al.*, 2000). Accordingly, the current results suggest left-brain dominance of ApEn corresponds to right-eye preference in predatory responses. Our results are also consistent with the idea that measures of the correlation dimension or related complexity increase with the difficulty of cognitive tasks (Bizas *et al.*, 1999; Micheloyannis *et al.*, 2002; Tomberg, 1999). Notably, EEG entropy increases with information processing demands during tasks involving visual recognition (Hogan *et al.*, 2012), arithmetic (Zarjam *et al.*, 2013) and acoustic cognition (Sohn *et al.*, 2007), respectively. Higher values of entropy are believed to arise due to increased neuronal coupling and enhanced connectivity during cognitive processing (Inouye *et al.*, 1993; Inouye *et al.*, 1991). Thus, it seems reasonable to speculate that prey stimulus moved into the RVF of the subjects in a clockwise direction would elicit similar increased neuronal coupling and enhance neuronal connectivity in the left hemisphere, which would lead to increasing complexity (ApEn) in these brain areas.

Moreover, in the present results, significant differences between LVF and RVF could be found for behavioral data in males but not in females, suggesting sex difference exists in visual lateralization for predatory response. Furthermore, significant differences of APEn existed across brain regions in males but not in females. These results are consistent with the idea that sex differences can have important effects on the pattern of lateralization observed within a species (Bianki, 2014; Reddon and Hurd, 2008; Vallortigara *et al.*, 1994). The most prominent of the mechanisms explaining such differences is the variation in hormonal expression, i.e. hormones can influence sex differences in brain structure and behavior including visual lateralization (Bibost *et al.*, 2013). Alternatively, sex specific

variation in lateralization may also be indicative of differences in underlying motivational factors that likely relate to their underlying life-history priorities (Bibost *et al.*, 2013). In the future, it will be important to determine how variations in hormonal expression or motivational factor interact with visual lateralization in the music frogs.

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# Appendix



**Figure S1** An example showing the positions of 7 electrodes on the skull of a subject. There were 2 electrodes above the telencephalon, diencephalon and mesencephalon respectively, while the reference was above the cerebellum.

## Supplementary descriptions for Approximate entropy (ApEn)

Briefly, for a given time series $u(i)$, $i = 1,...,N$, form a sequence of vectors that are defined according to

$$X(i) = [u(i), u(i+1),...,u(i+m-1)], \ i = 1,...,N-m+1 \qquad (1)$$

The distance between vectors $X(i)$ and $X(j)$ can be calculated with

$$d[X(i), X(j)] = \max_{k=1,2,...,m} |u(i+k-1) - u(j+k-1)| \qquad (2)$$

For each $i \le N-m+1$, $N^m(i)$ is the number of $j$ in dimension $m$ (the embedding dimension of phase space) such that $d[X(i), X(j)] \le r$, then $C_i^m(r)$ can be defined as

$$C_i^m(r) = (N-m+1)^{-1} N^m(i) \qquad (3)$$

where $r$ is the tolerance (i.e. minimal distance between vectors $X(i)$ and $X(j)$).

Next compute the natural logarithm of each $C_i^m(r)$ and average these over $i$

$$\phi^m(r) = (N-m+1)^{-1} \sum_{i=1}^{N-m+1} \ln C_i^m(r) \qquad (4)$$

Then increase the embedding dimension, i.e. from $m$ to $m+1$. Repeat steps (3)~(4) to obtain $C_i^{m+1}(r)$ and $\phi^{m+1}(r)$.

Finally ApEn is computed by subtracting $\phi^{m+1}(r)$ from $\phi^m(r)$ as

$$ApEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r) \qquad (5)$$